Citation:

Iso H, Kobayashi M, Ishihara J, Sasaki S, Okada K, Kita Y, Kokubo Y, Tsugane S; JPHC Study Group. Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: The Japan Public Health Center-Based (JPHC) Study Cohort I. *Circulation*. 2006; 113(2): 195-202.

PubMed ID: 16401768

Study Design:

Prospective cohort study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To examine an association between high intake of fish and omega-3 polyunsaturated fatty acids and the risk of coronary heart disease.

Inclusion Criteria:

Subjects who did not report the following conditions at baseline:

- Myocardial infarction
- Angina pectoris
- Stroke
- Cancer.

Exclusion Criteria:

Subjects who reported the following conditions at baseline:

- Myocardial infarction
- Angina pectoris
- Stroke
- Cancer.

Description of Study Protocol:

Recruitment

Subjects were recruited from public health centers in the following Japanese cities/districts: Ninohe, Karumai, Yokote, Omonogawa, eight districts of Minami-Saku county, Gushikawa and

Onna.

Design

A self-administered food frequency questionnaire was distributed that included questions about demographic characteristics, medical history, smoking and drinking habits and diet. The 1990 food frequency questionnaire included 44 foods with four questions that assessed fresh fish, dried fish and fish products, whereas the 1995 follow-up questionnaire assessed 147 foods with 19 questions about fish intake. Each subject was asked how often in the previous month (in the 1990 questionnaire) or in the preceding year (in the 1995 questionnaire) that fish was consumed. A common unit or portion size for each food was specified in the 1995 questionnaire but not in the 1990 questionnaire. The researchers calculated the consumption of each food by multiplying the frequency score of consumption of each food with each portion size. For dietary intake of long-chain omega-3 polyunsaturated fatty acids, the researchers assigned grams per serving for the fish in the 1990 questionnaire, and specific values for each of the fish and fish products in the 1995 questionnaire. Acute coronary events were registered if they occurred after the date of return of the baseline questionnaire and before January 1, 2002. Death certificates and medical records were reviewed to assess coronary events.

Statistical Analysis

Statistical analyses were based on incidence rates of coronary heart disease during 11-year follow-up from 1990 to the end of 2001. The incidence rates of coronary heart disease were calculated according to total fish consumption or quintiles of intake of omega-3 polyunsaturated fatty acids. The hazard ratio with 95% confidence intervals was calculated after adjustment for baseline values of age; sex; smoking status; alcohol intake; body mass index; history of hypertension or diabetes; medication for hypercholesterolemia; education level; sports at leisure time; public health center; and quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, omega-6 polyunsaturated fat, cholesterol and total energy.

Data Collection Summary:

Timing of Measurements

Food frequency questionnaire in 1990 and follow-up questionnaire in 1995. Incidence of coronary heart disease measured up to the end of 2001.

Dependent Variables

Incidence of coronary heart disease.

Independent Variables

Intake of fish and omega-3 polyunsaturated fat.

Description of Actual Data Sample:

Initial N: 43,149 (20,665 men and 22,484 women)

Attrition (final N): 41,578 (19,985 men and 21,593 women)

Age: 40 years to 59 years

Ethnicity: Japanese

Location: Japanese cities, towns and districts of: Ninohe, Karumai, Yokote, Omonogawa, eight districts of Minami-Saku county, Gushikawa and Onna.

Summary of Results:

During 477,325 person-years of follow-up of 41,578 individuals (19,985 men and 21,593 women), the researchers documented 258 incident cases of coronary heart disease (207 men and 51 women), including 198 definite and 23 probable myocardial infarctions and 37 sudden cardiac deaths. These cases comprised 196 nonfatal and 62 fatal coronary events.

Selected Dietary Variables in Cohort of 41,578 Men and Women According to Quintiles of Fish and Omega-3 Polyunsaturated Fatty Acid Intake

	Quintile of Fish Intake 1 (Low)	Quintile of Fish Intake 2	Quintile of Fish Intake 3	Quintile of Fish Intake 4	Quintile of Fish Intake 5 (High)
Mean daily intake of polyunsaturated fatty acids (grams)	0.3	0.6	0.9	1.3	2.4
Median fish intake (grams per day)	23	51	78	114	180
Frequency of fish intake (times per week)	1.3	2.7	3.6	5	8.4
Number at risk	8,914	8,527	8,171	7,946	8,020

Age, Sex-Adjusted and Multivariable Hazard Ratio and 95% Confidence Intervals of Coronary Heart Disease According to Quintiles of Fish Intake

	Quintile of Fish Intake 1 (Low)	Quintile of Fish Intake 2	Quintile of Fish Intake 3	Quintile of Fish Intake 4	Quintile of Fish Intake 5 (High)	P for Trend
Coronary Heart Disease (Number of Cases)	78	46	52	45	37	

Coronary Heart Disease **Hazard Ratio (95% Confidence Interval)**	1	0.57 (0.4-0.83)	0.74 (0.52-1.05)	0.6 (0.42-0.87)	0.47 90.32-0.69)	0.001
Total Myocardial Infarction (Number of Cases)	71	46	42	37	25	
Total Myocardial Infarction **Hazard Ratio (95% Confidence Interval)**	1	0.63 (0.44-0.92)	0.65 (0.45-0.96)	0.55 (0.37-0.81)	0.35 (0.22-0.56)	<0.001
Total Myocardial Infarction Multivariable Hazard Ratio (95% Confidence Interval)	1	0.81 (0.54-1.20)	0.85 (0.55-1.31)	0.78 (0.48-1.27)	0.47 (0.26-0.85)	0.03
Definite Myocardial Infarction (Number of Cases)	69	39	35	33	22	
Definite Myocardial Infarction **Hazard Ratio (95% Confidence Interval)**	1	0.55 (0.37-0.82)	0.56 (0.37-0.84)	0.50 (0.33-0.76)	0.32 (0.20-0.51)	<0.001

Definite Myocardial Infarction Multivariable Hazard Ratio (95% Confidence Interval)	1	0.70 (0.46-1.07)	0.74 (0.47-1.16)	0.72 (0.44-1.21)	0.44 (0.24-0.81)	0.03
Sudden Cardiac Death (Number of Cases)	7	0	10	8	12	
Sudden Cardiac Death **Hazard Ratio (95% Confidence Interval)**	1	N/A	1.60 (0.61-4.21)	1.15 (0.42-3.17)	1.60 (0.63-4.06)	0.04
Sudden Cardiac Death **Multivariable Hazard Ratio (95% Confidence Interval)**	1	N/A	1.25 (0.42-3.70)	0.88 (0.27-2.89)	1.14 (0.36-3.63)	0.15
Nonfatal Coronary Events (Number of Cases)	67	41	36	31	21	
Nonfatal Coronary Events **Hazard Ratio (95% Confidence Interval)**	1	0.60 (0.41-0.89)	0.60 (0.40-0.89)	0.49 (0.32-0.74)	0.31 (0.19-0.51)	<0.001

Nonfatal Coronary Events **Multivariable Hazard Ratio (95% Confidence Interval)**	1	0.77 (0.51-1.16)	0.79 (0.5-1.24)	0.70 (0.42-1.18)	0.43 (0.23-0.81)	0.02

The risk of coronary heart disease was approximately 40% lower among subjects at the highest quintile of fish intake (eight times per week, or median intake of 180g per day) than among those at the lowest quintile (once per week, or median intake 23g per day).

Age, Sex-Adjusted, and Multivariable Hazard Ratio and 95% Confidence Intervals of Coronary Heart Disease According to Quintiles of Omega-3 Polyunsaturated Fatty Acid Intake

	Quintile of Fish Intake 1 (Low)	Quintile of Fish Intake 2	Quintile of Fish Intake 3	Quintile of Fish Intake 4	Quintile of Fish Intake 5 (High)	P for Trend
Coronary Heart Disease (Number of Cases)	83	44	48	45	38	
Coronary Heart Disease **Hazard Ratio (95% Confidence Interval)**	1	0.57 (0.39-0.82)	0.6 (0.42-0.86)	0.58 (0.40-0.83)	0.46 (0.32-0.68)	0.001
Total Myocardial Infarction (Number of Cases)	76	44	39	36	26	
Total Myocardial Infarction **Hazard Ratio (95% Confidence Interval)**	1	0.62 (0.43-0.89)	0.53 (0.36-0.79)	0.51 (0.34-0.75)	0.35 (0.22-0.55)	<0.001

Total Myocardial Infarction Multivariable Hazard Ratio (95% Confidence Interval)	1	0.77 (0.52-1.15)	0.68 (0.43-1.05)	0.66 (0.40-1.09)	0.43 (0.24-0.78)	0.02
Definite Myocardial Infarction (Number of Cases)	73	39	33	32	21	
Definite Myocardial Infarction **Hazard Ratio (95% Confidence Interval)**	1	0.57 (0.39-0.84)	0.47 (0.31-0.71)	0.47 (0.31-0.71)	0.29 (0.18-0.48)	<0.001
Total Myocardial Infarction **Multivariable Hazard Ratio (95% Confidence Interval)**	1	0.70 (0.46-1.07)	0.59 (0.37-0.94)	0.59 (0.35-1.01)	0.35 (0.18-0.66)	0.005
Sudden Cardiac Death (Number of Cases)	7	0	9	9	12	
Sudden Cardiac Death **Hazard Ratio (95% Confidence Interval)**	1	N/A	1.32 (0.49-3.55)	1.33 (0.49-3.57)	1.65 (0.65-4.19)	0.03

Sudden Cardiac Death **Multivariable Hazard Ratio (95% Confidence Interval)**	1	N/A	1.04 (0.34-3.16)	1.03 (0.32-3.37)	1.24 (0.39-3.98)	0.12
Nonfatal Coronary Events (Number of Cases)	73	38	34	31	20	
Nonfatal Coronary Events **Hazard Ratio (95% Confidence Interval)**	1	0.56 (0.38-0.82)	0.49 (0.32-0.73)	0.45 (0.30-0.69)	0.28 (0.17-0.46)	<0.001
Nonfatal Coronary Events **Multivariable Hazard Ratio (95% Confidence Interval)**	1	0.69 (0.45-1.05)	0.61 (0.38-0.97)	0.57 (0.34-0.98)	0.33 (0.17-0.63)	0.003
Fatal Coronary Events (Number of Cases)	10	6	14	14	18	
Fatal Coronary Events **Hazard Ratio (95% Confidence Interval)**	1	0.64 (0.23-1.76)	1.44 (0.64-3.24)	1.46 (0.65-3.29)	1.79 (0.82-3.87)	0.03

The reduced risk associated with dietary intake of fish and omega-3 polyunsaturated fatty acids was confined to nonfatal coronary heart disease, not fatal coronary heart disease or sudden cardiac

deaths. Lack of a significant association was found with fatal coronary heart disease and sudden cardiac death (multivariate adjusted).

Author Conclusion:

High consumption of fish (eight times per week or 180g per day) was associated with reduced risk of coronary heart disease, more specifically, myocardial infarction and nonfatal coronary heart disease, compared with a modest consumption of fish (once per week or 23g per day). Our results suggest that a high fish intake may add a further beneficial effect for the prevention of coronary heart disease among middle-aged individuals.

Reviewer Comments:

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes

2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	???
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	N/A

5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	N/A
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	Yes
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes

8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	Yes
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes